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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,691	08/30/2006	Lindsay Jane Bawden	620-418	2784

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EXAMINER
DENT, ALANA HARRIS

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
10/06/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,691	BAWDEN ET AL.	
	Examiner	Art Unit	
	Alana Harris Dent, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,6-14,20,25-33,35 and 44-48* is/are pending in the application.

5a) Of the above claim(s) *37-43* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3, 6-14, 20, 25-33, 35 and 44-48* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 7, 2011 has been entered.

2. Claims 1-3, 6-14, 20, 25-33, 35 and 37-48 are pending.

Claims 37-43, drawn to non-elected inventions are withdrawn from examination.

Claims 1-3, 6-14, 20, 25-33, 35 and 44-48 have been amended.

Claims 1-3, 6-14, 20, 25-33, 35 and 44-48 are examined on the merits to the extent the elected species are H4 Lys 16 (Ac) from Table 1 and H3 Lys 79 (Me) from Table 2.

Withdrawn Grounds of Objection

Specification

3. The attempt to incorporate subject matter into this application by reference to H3 Lys 79 (Me), SEQ ID NO: 11 is effective because of Applicants' arguments and corresponding references in the specification, see Remarks submitted January 7, 2011, pages 18 and 19.

Withdrawn Grounds of Rejection

Claim Rejections - 35 USC § 112

4. The ***NEW MATTER REJECTION*** of claims 1-3, 6-14, 20, 25-33, 35 and 44-48 under 35 U.S.C. 112, first paragraph set forth in the Action mailed July 7, 2010 (page 4), as failing to comply with the written description requirement is withdrawn in light of Applicants' arguments and corresponding references in the specification, see Remarks, pages 18 and 19.

New and Maintained Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 6-14, 20, 25-33, 35 and 44-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***THIS IS A NEW MATTER REJECTION***.

Applicants have amended claims 1, 7, 20 and 44 to include negative provisos not supported by the specification. Applicants have included recitations such as "...antibody binds specifically to histone H4 which is acetylated...and does not bind to histone H4 which is not acetylated at said lysine residue" and "wherein one of said…antibodies binds specifically to a histone which comprises a modification and does not bind to said histone in the absence of the modification, and the other of said first or second antibodies binds to a nucleosome and does not bind to said histone comprising the modification…". While Applicants state the revised claims are fully supported by the disclosure and the claims originally filed February 17, 2006, the Examiner

does not concur. The Examiner has reviewed the specification, as well as the claims as originally filed and does not see support for these negative provisos. Applicants are requested to point out by page, line or paragraph where support can be found for this new claim language in the specification or delete the new matter.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 7-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 7 reads on first and second antibodies, wherein one of the antibodies binds a histone that comprises a modification and does not bind said histone and the other antibody binds a nucleosome and does not bind a histone comprising the modification. Moreover, the last wherein clause on lines 10-12 reads on both, first antibody and second antibody binding a histone modification. According to lines 6-9 only one antibody binds a histone modification and not both antibodies. The claim is not clear and the metes and bounds cannot be determined.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 1-3, 6, 20, 25-32, 35 and 44-48 are rejected under 35 U.S.C. 102(e) as being anticipated by Allis(b) et al./ U.S. Patent Application Publication number 2005/0069931 A1 (effective filing date February 19, 2003). However, Allis(b) discloses assaying isolated nucleosomes from a patient's blood or serum for specific histone amino terminus modifications as diagnostic indicators of disease, such as cancer, see abstract; page 3, section 0044; page 4, section

0059; and page 5, section 0065. Anti-modified histone antibodies are used in the assay to identify a modified histone, as well as antibodies that are capable of binding and isolating nucleosomes, see page 3, section 0049. The antibody can be labeled, see page 5, section 0064. An antibody that binds histone H4 which is acetylated at a lysine residue corresponding to position 16 is disclosed, see Figure 1; and page 3, section 0050. "The identification of the modified histone in the blood may be indicative of a particular or disorder", such as cancer, see page 2, section 0033; and page 3, sections 0044 and 0049. Moreover, nucleosomes are immunoprecipitated and the associated DNA is purified, labeled and subjected to molecular analytical techniques, such as PCR and sequence analysis, see page 5, section 0061; and page 6, sections 0069 and 0070. Also taught in Allis(b) is the implementation of DNA microarrays and hybridization, see page 6, section 0068.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The rejection of claims 1-3, 6, 20, 25-33, 35 and 44-48 under 35 U.S.C. 103(a) as being unpatentable over Allis et al./ U.S. Patent Application Publication number 2006/0073517 A1 (effective filing date March 10, 2003), and further in view of Allis(b) et al./ U.S. Patent Application Publication number 2005/0069931 A1 (effective filing date February 19, 2003) is maintained. Applicants assert the antibodies of the claimed invention bind exclusively to H4 Lys 16 (Ac) and H3 Lys 79 (Me) and "Allis is totally silent about any association between H4 Lys 16 (Ac) and/or H3 Lys 79 (Me) and diseases, likewise, the association between disease and the identification of these marks in cell-free samples", see Remarks, page 20. Applicants further assert Allis(b) fails to remedy the alleged deficiencies of Allis and hence the claimed invention would not have been obvious, see Remarks, page 21. Applicants also argue neither Allis reference teaches a two antibody immunoassay. These points of view, as well as the accompanying arguments have been carefully considered, but found unpersuasive.

Applicants are reminded once again the claims do not read on antibodies that bind exclusively to H4 Lys 16 (Ac) and H3 Lys 79 (Me). Moreover, the phrase "specifically binds" is given its broadest reasonable interpretation and the phrase defines the act of an antibody binding to its antigenic determinant/epitope. The term "specifically" is not interpreted to mean "exclusivity". The antigen of the prior art is related to Applicant's antigen and the prior art antibodies would at the least cross-react.

The antibodies of Allis are able to bind modified histones associated with a disease state contrary to Applicants' assertions, see page 11, section 0094. The antibodies of Allis specifically bind only histones that comprise a modified sequence, see page 11, section 0092. These sequences include H3 Lys 79 (Me) and H4 Lys 16 acetyl, see page 8, sections 0072 and 0075, respectively. Teachings within Allis of suppressor binding and bromodomain of Gen5 do not preclude the teachings of antibodies specific for methylated and acetylated amino acid residues. Allis teaches a method of detecting chromatin alterations…associated with a disease state, wherein chromatin from both normal and diseased tissues are contacted with an antibody, see page 19, claim 24. The staining pattern and detectable differences of the antibody bound chromatin isolated from normal tissue to the staining pattern of the antibody bound chromatin isolated from the diseased state is implemented in diagnosing disease. The diagnostic assay includes antibodies linked to

detectable labels and attached to a solid support, see page 11, sections 0093 and 0095. Allis further teaches the implementation of a two-site immunoassay, see page 12, section 0099. Allis does not teach the claimed method, wherein a biological fluid sample is obtained from an individual and the disease condition is a cancer or an autoimmune disease. Allis also does not teach the claimed method, wherein DNA associated with the nucleosome comprising a modified histone is isolated, amplified and sequenced and a two-site assay.

However, Allis(b) teaches assaying isolated nucleosomes from a patient's blood or serum for specific histone amino terminus modifications as diagnostic indicators of disease, such as cancer, see abstract; page 3, section 0044; page 4, section 0059; and page 5, section 0065. Anti-modified histone antibodies are used in the assay to identify a modified histone, as well as antibodies that are capable of binding and isolating nucleosomes, see page 3, section 0049. Moreover, nucleosomes are immunoprecipitated and the associated DNA is purified, labeled and subjected to molecular analytical techniques, such as PCR and sequence analysis, see page 5, section 0061; and page 6, sections 0069 and 0070. Also taught in Allis(b) is the implementation of DNA microarrays and hybridization, see page 6, section 0068. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made based on both references to assess nucleosomes and modified histone proteins in a number of biological fluids and conduct protein and nucleic acid based

assays in order to diagnose diseases. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both Allis references to assay specific histone modifications because they serve as diagnostic markers of disease, see Allis page 1, section 0010; and Allis(b) page 1, sections 0007 and 0008.

For the reasons of record and reiterated herein the rejection is maintained.

13. Claims 1-3, 6, 20, 25-33, 35 and 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feng et al. (Current Biology 12: 1052-1058, June 25, 2002), and further in view of Allis(b) et al./ U.S. Patent Application Publication number 2005/0069931 A1 (effective filing date February 19, 2003). Feng teaches an antibody specific for H3-mK79, see bridging sentence of pages 1052 and 1054. Feng does not teach the claimed method, wherein a biological fluid sample is obtained from an individual and the disease condition is a cancer or an autoimmune disease. Feng also does not the claimed method, wherein DNA associated with the nucleosome comprising a modified histone is isolated, amplified and sequenced.

However, Allis(b) teaches assaying isolated nucleosomes from a patient's blood or serum for specific histone amino terminus modifications as diagnostic indicators of disease, such as cancer, see abstract; page 3, section 0044; page

4, section 0059; and page 5, section 0065. Anti-modified histone antibodies are used in the assay to identify a modified histone, as well as antibodies that are capable of binding and isolating nucleosomes, see page 3, section 0049. Moreover, nucleosomes are immunoprecipitated and the associated DNA is purified, labeled and subjected to molecular analytical techniques, such as PCR and sequence analysis, see page 5, section 0061; and page 6, sections 0069 and 0070. Also taught in Allis(b) is the implementation of DNA microarrays and hybridization, see page 6, section 0068. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made based on both references to assess nucleosomes and modified histone proteins in a number of biological fluids and conduct protein and nucleic acid based assays in order to diagnose diseases. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in both Allis references to assay specific histone modifications because they serve as diagnostic markers of disease, see Allis page 1, section 0010; and Allis(b) page 1, sections 0007 and 0008.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Alana Harris Dent, Ph.D. whose telephone number is (571)272-0831. The Examiner works a ***flexible schedule***,

however she can normally be reached on 8 am to 8 pm, Monday through Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Misook Yu, Ph.D. can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alana Harris Dent, Ph.D.
20 September 2011
/Alana Harris Dent, Ph.D./

Primary Examiner, Art Unit 1643